Exhibit 3

Quality Management Essentials

Expert Advice on Building a Compliant System

FDANEWS

Quality Management Essentials

Expert Advice on Building a Compliant System

Table of Contents

Introduction

A strong quality management system is the foundation of a drug manufacturer's success. But a shaky quality system is sure to lead to a company's downfall.

In this report, top authorities in quality management give insight and advice on the features that make a system strong and effective. This collection of essays from five of the drug industry's most knowledgeable practitioners illustrates exactly how to create – or update – a quality management system that hits all the right notes in the areas of:

- Corporate leadership;
- Risk assessment;
- Root cause analysis and investigations;
- Training and communications;
- Internal auditing; and
- Managing suppliers and contractors.

These five experts average more than three decades of experience (two of them spent 25+ years at the FDA) in developing effective quality systems. Step into their "classrooms" and let them teach you what they know.

David Chesney, Principal and General Manager, DL Chesney Consulting LLC, looks at the role of upper management in promoting and maintaining quality.

Lori Richter, Senior Consultant, Valsource, writes about risk assessment – what it is, how and when to use it, and how it can build a strong foundation for quality.

James Vesper, Director, Valsource Learning Solutions, looks at conducting investigations, analyzing findings and getting to the root cause of a problem.

Susan Schniepp, Fellow, Regulatory Compliance Associates, Inc., takes on the elements of a good training program, as well the benefits of internal auditing.

Steven Sharf, President, GMP Concepts, shares his knowledge of best practices in working with vendors, suppliers and contractors.

Executive Responsibility for Quality

By David L. Chesney, Principal and General Manager, DL Chesney Consulting, LLC

The purpose of this article is to summarize current global good manufacturing practice (GMP) compliance and quality management responsibilities of executives in the pharmaceutical industry as well as how GMP expectations are applied through policies of the FDA. It includes some suggestions for executive management teams that will help ensure that requirements and expectations of health regulatory authorities are met and that the company's regulatory risk is minimized.

Importance of Quality

Executive commitment to quality in the pharmaceutical industry is critical, not only to ensure continuing profitability of the company, but also for the safety and well-being of patients and to meet the needs of healthcare providers who prescribe and use pharmaceutical products every day.

In other industries, the connection between high-quality products and sales performance is typically more direct and measurable. Japan has for many years been a world leader in quality management. Consumer products from Japan, such as automobiles and electronic products, enjoy a world-class reputation for high quality that translates directly to sales and business success.

That connection is not as clear in the pharmaceutical industry. While healthcare professionals may have preferences, patients normally do not play much of a role in product choice and, if they do, the basis for their influence is more likely to come from advertising than from a perception of quality of a specific company's product compared to competing choices. For new products, market exclusivity limits competition for the duration allowed by law, depending on the country where the product is sold. Where it exists, patent exclusivity can diminish management's perception that maintenance of quality is critical to ongoing business success.

For these reasons, quality assurance (QA) and GMP compliance may be viewed differently in the pharmaceutical industry than in those industries where a reputation for high quality drives sales. QA may be viewed as a "cost of doing business" or an internal "police department" issuing directives that delay or prevent product release. That viewpoint can result in a low priority being assigned to quality operations and resourcing, which can lead in turn to quality problems, regulatory difficulties, unnecessary expense, adverse publicity, lawsuits and investor disappointment. All these consequences are preventable if executive managers understand the importance of the QA function and treat it as a critical business operation just like other critical areas, such as strategic planning, financial management and others.

A sophisticated, properly managed and well-resourced QA program provides many direct benefits to a business, including, but not limited to:

- Avoidance of regulatory problems and delays in approval of new products;
- Prevention of loss of product failing to meet release specifications;
- Prevention of adverse reactions resulting from quality defects;

- Prevention of patient lawsuits resulting from quality problems;
- Avoidance of adverse publicity and loss of investor confidence; and
- Assurance of reliable, consistent supply of product to meet market demands.

Regulatory Considerations

In addition to the business benefits, health regulatory agencies around the world both require and expect top management to support a strong QA function for their companies.

In the U.S., this principle has been in effect for decades. The first legal case that firmly established the responsibility of executive management was the 1943 U.S. Supreme Court case *U.S. v. Dotterweich.*[1] Mr. Dotterweich's company, Buffalo Pharmacal, was inspected by the FDA, resulting in direct adulteration and misbranding findings. The FDA criminally prosecuted Mr. Dotterweich and the company, charging that as president, he was ultimately responsible for the company's actions and therefore should be found guilty of violating the law.

Following a District Court case and subsequent appeal, the Supreme Court ruled on his case and concluded that as president, he could be held responsible for the acts of the corporation even though he did not know of the violations and did not intend for them to occur. This has become known in the U.S. as the Doctrine of Strict Liability, or "Responsible Corporate Officer" doctrine.[2] It applies to those who, in the words of the Court, "…stand in a responsible relationship to the acts of the corporation."[3]

In 1975, this concept once again came before the U.S. Supreme Court in a case involving John R. Park, President of Acme Wholesale Grocery Company, a retail grocery chain.[4] The case involved insanitary conditions in Acme's food warehouses. Mr. Park was, like Mr. Dotterweich, charged with criminal violations of the Food, Drug and Cosmetic Act for failures of the company to control the insanitary conditions. Like Mr. Dotterweich, Mr. Park defended himself by claiming that he was not involved in the conduct that violated the law and that he had delegated authority to "dependable subordinates" he trusted to do the right thing. As in the *Dotterweich* case, the Court affirmed Mr. Park's conviction. In the majority opinion in this case, the Court said:

> "*The Act imposes not only a positive duty to seek out and remedy violations when they occur but also, and primarily, a duty to implement measures that will ensure that violations will not occur.*"
>
> *"The requirements of foresight and vigilance imposed on responsible corporate agents are beyond question demanding and even onerous, but they are no more stringent than the public has the right to expect… We are satisfied that the Act imposes the highest standard of care and permits conviction of responsible corporate*

[1] *U.S. v. Dotterweich*, 320 U.S. 277 (1943).

[2] Under the Food, Drug and Cosmetic Act, strict liability only applies to misdemeanor charges. Felonies require evidence of intent or a repeat violation.

[3] *U.S. v. Dotterweich*, supra.

[4] *U.S. v. Park,* 421 U.S. 658 (1975).

officials, who in light of this standard of care, have the power to prevent or correct violations."[5]

The *Park* case has, to date, settled the question in the U.S. about the legal responsibility of executive management in the pharmaceutical industry. Today, while criminal prosecutions still take place, more commonly we see the concept of executive managerial responsibility emerging in FDA Warning Letters,[6] which are most often addressed to the president or CEO of a company, and the naming of individual defendants, in their personal capacity, in consent decrees of permanent injunction. These examples serve to illustrate that the FDA places ultimate responsibility for the acts of a corporation on the senior level executives of that corporation.

Other countries' laws vary and may not embody strict liability principles as the U.S. system does, but other principles do apply, most importantly those in the International Council on Harmonization (ICH) guideline Q10 – *Pharmaceutical Quality System* (see Appendix A). Worldwide, ICH guidelines are highly influential in pharmaceutical quality and regulatory compliance.

In summary, ICH Q10 recommends that executive management demonstrate a commitment to quality that includes certain key principles, which it lists in detail. ICH Q10 further recommends that the actions that should be taken by executive management to accomplish its stated objectives include:

- Establish a strong quality policy;
- Support and participate in quality planning;
- Determine and provide adequate and appropriate resources (human, financial, materials, facilities and equipment) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness;
- Ensure appropriate internal communication processes are established and implemented within the organization; and
- Be responsible for pharmaceutical quality system governance through management review to ensure its continuing suitability and effectiveness.

It's not easy to give a simple answer to the question of what executive management teams need to do to implement these principles. The way these principles should be implemented varies mainly with the size and global reach of the company. What works in practice for a small, one-site company will differ in many ways from what a large, diverse global company's top management team needs to do. With that understanding, here are some general suggestions that apply to all companies in this industry, regardless of size or complexity. The details need to be worked out in each specific case with these principles in mind:

1. Executive managers must recognize the criticality of a strong QA organization and quality system to patient safety and to the company's business success;

[5] Id.

[6] Chesney, David L. "Warning Letter: An Enforcement Tool in Need of Balance," *Update* Magazine, Food and Drug Law Institute, September/October 2010.

2. Quality management must be seen as similar to other critical business management activities executives participate in, such as strategic planning, budget management, succession planning and other areas;
3. Executive management teams must support their QA organization with authority and resources that are equal to the responsibility they have. Systems and organizational reporting structures must assure that the quality unit can make decisions without undue influence from other organizational components and avoid conflict of interest;
4. Executive management must establish a strong quality policy that makes it clear the company is committed to consistently producing high-quality products that perform clinically as intended. Day-to-day statements and actions of top level executives must demonstrate that this commitment is real, not just words on paper.
5. As with other management responsibilities, executive teams must be kept aware of the performance of the quality system and of any emerging problems that are being dealt with. The key to doing this successfully starts with meaningful metrics, produced at a frequency that will enable early intervention (at a minimum, quarterly, or better, monthly).

Common Mistakes Executive Teams Make

In our consulting practice, we often are called upon to assist when a problem has occurred. Frequently, a regulator has discovered the problem and there is concern that the regulator may escalate its response or take a formal enforcement action. Some of the common mistakes that lead to this situation include, but are not limited to:

1. Failure to have an independent quality unit that is empowered to make the decisions that must be made to ensure compliance;
2. Under-resourcing of the quality unit, resulting in a lack of necessary talent, numbers of personnel or support tools to perform adequately;
3. Emphasizing production quotas and market demands to the extent that quality problems are overlooked or regarded as unimportant – worst case, deliberate cover-up of known quality problems through falsification of records; and
4. Failure to understand current regulatory requirements and expectations for each part of the world where the company's products are sold.

Each of these issues, and others, are avoidable through education of executive management and ongoing management review of the quality system.

Summary

The pharmaceutical industry is globalized as never before in history. Requirements and expectations of health regulatory authorities may differ somewhat, but through international bodies such as ICH, regulators are achieving growing consensus about the most critical quality management concepts. First among those is that executive management teams are the key to a company's ability to successfully meet quality standards on a consistent basis. Doing so is critical to proper clinical performance of the products of this industry and therefore, ultimately, to global public health.

Prudent management teams recognize this and support their quality units both philosophically and materially, with strong policies backed up by consistent actions, authority and resources. Failure to do so may have both serious business consequences for the company and potentially even personal consequences for individual executives.

About the Author

David L. Chesney is Principal and General Manager of DL Chesney Consulting, LLC. He served with the FDA for 23 years in four different FDA District Offices, ending his career as District Director in the San Francisco Office. Subsequently, he served with PAREXEL Consulting for 21 years, 19 of which he was the Vice President and Practice Lead for the Strategic Compliance Consulting unit, providing GMP and GCP consulting services worldwide. In 2016, he founded DL Chesney Consulting, LLC, and currently provides GMP and GCP consulting services to pharmaceutical companies throughout the world.

Mr. Chesney holds a Bachelor's Degree in Life Science from California State University, Northridge, and completed three years postgraduate study in life sciences there and at California State University San Diego. He also holds Certificates in Health Care Compliance and Pharmaceutical Law from Seton Hall University School of Law, where he is currently completing a Master of Science in Jurisprudence degree, concentrating in Pharmaceutical and Medical Device Law. He is an active member of the Parenteral Drug Association, the Food and Drug Law Institute and the Regulatory Affairs Professionals Society.